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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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HOGAN & HARTSON L.L.P.
1999 AVENUE OF THE STARS
SUITE 1400
LOS ANGELES, CA 90067

EXAMINER	
AEDER, SEAN E	
ART UNIT	**PAPER NUMBER**
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/713,808	HOON ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/15/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10 and 31-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10 and 31-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/15/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Request for Continued Examination

The request filed on 12/15/06 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 10/713,808 is acceptable and a RCE has been established. An action on the RCE follows..

Claims 34-35 have been newly added.

Claims 1 and 5-7 have been amended by Applicant.

Claims 1-7, 10, and 31-35 are pending and are currently under consideration.

Rejections Withdrawn

The rejections of 1-7, and 10 under 35 U.S.C., second paragraph, are withdrawn.

The rejection of claims 1-4, 6, 7, and 10 under 35 U.S.C. first paragraph, for failing to comply with the written description requirement (new matter), is withdrawn.

Response to Arguments

35 USC § 112, first paragraph (enablement rejection)

Claims 1-7, and 10 remain rejected and newly added claims 34-34 are rejected under 35 U.S.C. first paragraph, for failing to comply with the enablement rejection for the reasons stated in the Office Action of 9/15/06 and for the reasons set-forth below.

The Office Action of 9/15/06 contains the following text:

"while being enabling for a method for melanoma prognosis comprising isolating nucleic acid from sentinel lymph node samples and blood samples obtained from a

melanoma patient and amplifying nucleic acid targets comprising GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase, wherein an increase in expression of said targets, as compared to expression of said targets in corresponding normal lymph tissue or normal blood samples, is indicative of an increase in metastatic melanoma recurrence, a decrease in metastatic-melanoma free survival, and a decrease in patient survival, does not reasonably provide enablement for a method for melanoma prognosis comprising isolating nucleic acid from just *any* biological sample from a melanoma patient deemed "associated with melanoma" and amplifying nucleic acid targets comprising GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase, wherein *any* level of said targets is indicative of melanoma recurrence, survival without any kind of disease, and overall survival. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are drawn to a method for melanoma prognosis comprising isolating nucleic acid from just *any* biological sample from a melanoma patient deemed

"associated with melanoma" and amplifying nucleic acid targets comprising GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase, wherein *any* level of said targets is indicative of melanoma recurrence, survival without any kind of disease, and overall survival. The claims are further drawn to selecting treatment regimes based on said prognosis. It is noted that the claims broadly read on using any biological sample in the method, as it is not clear what would prevent a biological sample from being deemed "associated with melanoma". Further, the claims broadly read on any level of said targets being indicative of melanoma recurrence, survival without any kind of disease, and overall survival. Clearly, levels that are indicative of an increase in melanoma recurrence, a decrease in survival without any kind of disease, and a decrease in overall survival, for example, would not be indicated of a decrease in melanoma recurrence, an increase in survival without any kind of disease, and an increase in overall survival.

The specification discloses a method for melanoma prognosis comprising isolating nucleic acid from sentinel lymph node samples obtained from a melanoma patient and amplifying nucleic acid targets comprising GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase, wherein an increase in expression of said targets, as compared to expression of said targets in corresponding normal lymph tissue is indicative of an increase in metastatic melanoma recurrence (Figure 4), a decrease in metastatic-melanoma free survival (Table 5), and a decrease in patient survival (Figure 5) (see pages 25-30, in particular). Further, the samples the specification *prophetically* discloses to use with the claimed method consist of paraffin-embedded (PE) melanoma

tissues, frozen lymph nodes, and PE lymph nodes (page 6 lines 21-24, in particular). Further, the specification provides no guidance, working examples, or exemplification demonstrating how detecting the expression of the target genes in a sample could be used to "select" any particular treatment regime from those commonly used to treat any metastatic melanoma.

Further, post-filing art teaches that the expression levels of a panel of marker genes including GalNAct and PAX3 in blood samples from melanoma patients are predictive of melanoma recurrence, disease-free survival, and overall survival (see page 8575 of Koyanagi et al (2005) J Clin Oncol 23(31):8057-8064).

The state of the prior art dictates that if an increase or decrease in expression of molecules such as nucleic acids encoding GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase are to be used as surrogates for a diseased state, some disease state must be identified in some way with either an increase or a decrease in the expression of the molecules. There must be some expression pattern that would allow the markers to be used in a diagnostic manner. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated

(emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence of the markers' expression including the correlation to a diseased state, one of skill in the art would not be able to predictably use the markers in any diagnostic setting without undue experimentation. In the instant case, it is apparent that an increase in expression of GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase in sentinel lymph node samples and blood samples from melanoma patients, as compared to corresponding normal lymph tissue or normal blood samples, is indicative of an increase in metastatic melanoma recurrence, a decrease in metastatic-melanoma free survival, and a decrease in patient survival.

However, the level of unpredictability for prognosticating diseases is quite high. Since neither the specification nor the prior art provide evidence of a universal

association between the claimed method and every type of sample, a practitioner wishing to practice the claimed invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method for melanoma prognosis comprising isolating nucleic acid from just *any* biological sample from a melanoma patient deemed "associated with melanoma" and amplifying nucleic acid targets comprising GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase, wherein *any* level of said targets is indicative of melanoma recurrence, survival without any kind of disease, and overall survival, and Applicant has not enabled said method of prognosis because it has not been shown that *any* level of said targets in just any biological sample is indicative of melanoma recurrence, survival without any kind of disease, and overall survival. Further, the specification is not enabling for selecting any treatment regime based on any prognosis (claim 11), as the specification provides no guidance, working examples, or exemplification demonstrating how detecting the expression of said target genes in a sample could be used to "select" any particular treatment regime from those commonly used to treat any metastatic melanoma.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed."

In response to the Office Action of 9/15/06, Applicant amended claim 1 to recite "a sentinel lymph node (SLN) sample" and "wherein, as compared to control levels, an increase in the levels of the nucleic acid targets is indicative of an increase in melanoma recurrence, a decrease in disease-free survival, or a decrease in overall survival, and a decrease in the levels of the nucleic acid targets is indicative of a decrease in melanoma recurrence, an increase in disease-free survival, or an increase in overall survival". It is further noted that a declaration by Dave Hoon states that non-sentinel lymph node (NSLN) samples from 22 patients were evaluated. 11 of the 22 patients were upstaged by multimarker qRT of the NSLN. The declaration further states that of the 11 patients whose disease recurred during long-term follow-up, 8 patients had been "molecularly upstaged". Further, it is noted that the declaration and the specification do not indicate whether patients whose disease did not recur were "molecularly upstaged". The declaration further states that NSLN samples can be used in a method comprising amplifying nucleic acid targets from GalNAcT and/or PAX3 genes and detecting the levels of said nucleic acid targets and predicting melanoma recurrence, disease-free survival, overall survival, or a combination thereof, based on the levels of the nucleic acid targets, wherein, as compared to control levels, an increase in the lvels of the nucleic acid targets is indicative of an increase in melanoma recurrence, a decrease in disease-free survival, or a decrease in overall survival, and a decrease in the levels of the nucleic acid targets is indicated of a decrease in melanoma recurrence, an increase in disease-free survival, or an increase in overall survival.

The amendments to the claims have been carefully considered, but are not deemed persuasive. While being enabling for a method for melanoma prognosis comprising isolating nucleic acid from sentinel lymph node samples and blood samples obtained from a first melanoma patient and amplifying mRNA transcripts encoded by GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase genes from said nucleic acid, wherein a higher level of mRNA transcripts encoded by GalNAcT, PAX3, MART-1, MAGE-A3, and Tyrosinase genes in nucleic acid from sentinel lymph node samples and blood samples obtained from a first melanoma patient, as compared the level of mRNA transcripts encoded by GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase genes in nucleic acid from sentinel lymph node samples or blood samples from a second patient with melanoma indicates that said first melanoma patient has an increased probability of metastatic melanoma recurrence, a decreased probability of metastatic-melanoma free survival, and a decrease in overall survival as compared to said second melanoma patient, and wherein a lower level of mRNA transcripts encoded by GalNAcT, PAX3, MART-1, MAGE-A3, and Tyrosinase genes in nucleic acid from sentinel lymph node samples and blood samples obtained from a first melanoma patient, as compared the level of mRNA transcripts encoded by GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase genes in nucleic acid from sentinel lymph node samples or blood samples from a second patient with melanoma indicates that said first melanoma patient has a decreased probability of metastatic melanoma recurrence, and an increased probability of metastatic-melanoma free survival, and an increase in overall survival as compared to said second melanoma patient, the specification is NOT enabling for a method of

melanoma prognosis comprising isolating nucleic acids from just any sample (including NSLN samples) obtained from a melanoma patient and amplifying just any type of nucleic acid targets from GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase, wherein an increase in expression of said targets, as compared to expression of said targets in just any control, is indicative in just any way of an increase in metastatic melanoma recurrence, a decrease in metastatic-melanoma free survival, and a decrease in patient survival as compared to just anyone else *and a decrease in the levels of the nucleic acid targets is indicative in just any way of a decrease in melanoma recurrence, an increase in disease-free survival, or an increase in overall survival as compared to just anyone else.*

In regards to performing the claimed method using NSLN samples, the specification does not demonstrate that NSLN samples could be used in the claimed method with any predictability of success. The declaration of Dave Hoon indicates that of the 11 patients whose disease recurred during long-term follow-up, 8 patients had been "molecularly upstaged" using NSLN samples; however, it has not been demonstrated that there is a difference between levels of detected GalNAcT, PAX3, MART-1, and MAGE-A3 nucleic acids in NSLN samples in melanoma patients who exhibit metastatic melanoma recurrence and melanoma patients that exhibit disease-free survival.

In regards to using just any control sample in the claimed method, the claimed method would not predictably function with just any control. Limitations disclosed in the specification, as to what one would use as a control, are not read into the claims. One

of skill in the art would recognize that possible controls include corresponding samples derived from melanoma patients that have exhibited metastatic melanoma recurrence, melanoma patients that have not exhibited metastatic melanoma recurrence, and corresponding samples derived from disease-free patients. As broadly claimed, one of skill in the art would recognize that the specification is not enabled for a method wherein an increase in expression of GalNAcT, PAX3, MART-1, and MAGE-A3 nucleic acid targets in SNL and blood samples of melanoma patients, as compared to expression of said targets in controls of corresponding lymph tissue or blood samples from melanoma patients that have exhibited metastatic melanoma recurrence, is indicative of an increase in metastatic melanoma recurrence, a decrease in metastatic-melanoma free survival, and a decrease in overall survival. Further, one of skill in the art would recognize that the specification is not enabled for a method wherein a decrease in expression of GalNAcT, PAX3, MART-1, MAGE-A3, and Tyrosinase nucleic acid targets in SNL and blood samples of melanoma patients, as compared to expression of said targets in controls of corresponding lymph tissue or blood samples from healthy individuals, would predictably be indicative of an increase in metastatic melanoma recurrence, a decrease in metastatic-melanoma free survival, and a decrease in melanoma recurrence, an increase in disease-free survival, or an increase in overall survival. However, the specification supports a method for melanoma prognosis comprising isolating nucleic acid from sentinel lymph node samples and blood samples obtained from a first melanoma patient and amplifying mRNA transcripts encoded by GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase genes from said nucleic acid,

wherein a higher level of mRNA transcripts encoded by GalNAcT, PAX3, MART-1, MAGE-A3, and Tyrosinase genes in nucleic acid from sentinel lymph node samples and blood samples obtained from a first melanoma patient, as compared the level of mRNA transcripts encoded by GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase genes in nucleic acid from sentinel lymph node samples or blood samples from a second patient with melanoma indicates that said first melanoma patient has an increased probability of metastatic melanoma recurrence, a decreased probability of metastatic-melanoma free survival, and a decrease in overall survival as compared to said second melanoma patient, and wherein a lower level of mRNA transcripts encoded by GalNAcT, PAX3, MART-1, MAGE-A3, and Tyrosinase genes in nucleic acid from sentinel lymph node samples and blood samples obtained from a first melanoma patient, as compared the level of mRNA transcripts encoded by GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase genes in nucleic acid from sentinel lymph node samples or blood samples from a second patient with melanoma indicates that said first melanoma patient has a decreased probability of metastatic melanoma recurrence, and an increased probability of metastatic-melanoma free survival, and an increase in overall survival as compared to said second melanoma patient (Figure 4, in particular).

It is further noted that the term "nucleic acid targets from a panel of marker genes..." broadly reads on "mRNA transcripts encoded by a panel of marker genes", "genomic DNA comprising a panel of marker genes", and "genomic sequences regulated by proteins encoded by proteins encoded by a panel of marker genes". Since the specification only demonstrates a relationship between mRNA transcripts encoded

by a panel of marker genes comprising GalNAcT, PAX3, MART-1, MAGE-A3, and Tyrosinase genes and melanoma prognosis, it would require undue experimentation in order to determine whether there is a relationship between levels of genomic DNA comprising GalNAcT, PAX3, MART-1, MAGE-A3, and Tyrosinase genes and a melanoma prognosis (i.e. if amplification of GalNAcT, PAX3, MART-1, MAGE-A3, and Tyrosinase genes is related to a melanoma prognosis). Further, since all genomic sequences regulated by proteins encoded by proteins encoded GalNAcT, PAX3, MART-1, MAGE-A3, and Tyrosinase genes have not been disclosed or identified, it would require undue experimentation to identify said genomic sequences and determine whether regulation of said genomic sequences is related to melanoma prognosis.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as broadly claimed.

35 USC § 103(a)

Claims 31-33 are rejected under 35 U.S.C. 103(a) for being unpatentable over Palmieri et al (March 2001, Journal of Clinical Oncology, 19(5):1437-1443) in view of Scholl et al (February 2001, Cancer Research, 61:823-826) and Kuo et al (February 1998, Clinical Cancer Research, 4:411-418) for the reasons stated in the Office Action of 9/15/06 and for the reasons set-forth below.

The Office Action of 9/15/06 contains the following text:

"Claim 31 is drawn to a method comprising obtaining a sentinel lymph node (SNL) sample from a melanoma patient, wherein the sample is histopathologically negative for melanoma cells; isolating nucleic acid from the sample; amplifying nucleic acid targets from a panel of marker genes, wherein the panel comprises GalNAct, PAX3, or both; and detecting the levels of the nucleic acid targets. Claim 32 is drawn to the method of claim 31, wherein the panel further comprises marker genes selected from the group consisting of MAGE-A3, MART-1, and Tyrosinase. Claim 33 is drawn to the method of claim 32, wherein the panel comprises a first combination of MAGE-A3, GalNAcT, MART-1, and PAX3; or a second combination of Tyrosinase, MART-1, GalNAcT, and PAX3.

Palmieri et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from sentinel lymph node samples obtained from a patient, using RT-PCR to isolated nucleic acids and amplify mRNA targets from a panel of marker genes comprising MART-1 and tyrosinase (pages 1438-1439, in particular). The methods taught by Palmieri et al comprise methods wherein the sentinel lymph

node samples are histopathologically negative for melanoma cells (paragraph bridging the left and right columns of page 1438), wherein the histopathology is determined by hematoxylin and eosin staining and immunohistochemistry. Palmieri et al further teaches, and one of skill in the art would recognize, that multiple-marker assays are more sensitive and specific than single-marker assays in detecting metastatic melanoma cells (page 1441 right column, in particular).

Palmieri et al does not specifically teach methods of detecting metastatic melanoma cells comprising isolating nucleic acids from sentinel lymph node samples obtained from a patient, using RT-PCR to isolated nucleic acids and amplify mRNA targets from a panel of marker genes comprising MAGE-A3, GalNAcT and/or PAX3. However, these deficiencies are made up in the teachings of Scholl et al (February 2001, Cancer Research, 61:823-826) and Kuo et al (February 1998, Clinical Cancer Research, 4:411-418).

Scholl et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, amplifying nucleic acid targets from a panel of marker genes comprising PAX3, MAGE-A3, and tyrosinase and detecting the presence or absence of the nucleic acid targets (Table 1 and Table 2, in particular).

Kuo et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, amplifying nucleic acid targets from a panel of marker genes comprising GalNAcT and detecting the presence or absence of GalNAcT (page 413 right column, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to detect metastatic melanoma cells comprising a method of isolating nucleic acids from histopathologically negative sentinel lymph node samples obtained from a patient, using RT-PCR to isolated nucleic acids and amplify mRNA targets from a panel of marker genes comprising MART-1 and tyrosinase as taught by Palmieri et al and also amplify any other genes associated with metastatic melanoma, such as those taught by Sholl et al (PAX3 and MAGE-A3) and Kuo et al (GalNAcT). Further, one would have been motivated to do so because multiple-marker assays are more sensitive and specific than single-marker assays in detecting metastatic melanoma cells. Further, one of skill in the art would have a reasonable expectation of success in performing the claimed method since detection of genes is well known and conventional in the art."

In response to the Office Action of 9/15/06, Applicant states: "Although Palmieri indicates that the RT-PCT assay shows good sensitivity for Tyrosinase and MART-1 markers in histopathologically negative SLN samples, it does not teach that every marker would be detectable by an RT-PCR assay in histopathologically negative SLN samples. Neither Scholl nor Kuo indicates that PAX3 or GalNacT would be detectable by an RT-PCR assay in histopathologically negative SLN samples. It is well known in the art that each gene has a unique expression patter. The timing, location, and level of expression varies from gene to gene. Given the high unpredictability, even if one skilled in the art would have been motivated to combine Palmieri with Scholl and Kuo, there would have been no reasonable expectation of success in detecting PAX3 or GalNacT

by an RT-PCR assay in histopathologically negative SLN samples, because for example the level of PAX3 or GalNacT might have been too low to be detected by RT-PCR due to either low expression of the gene or dilution of the marker by other mRNAs...Furthermore, claim 31 is non-obvious over the cited art because the method of claim 31 has unexpected advantages. More specifically, it is the discovery of the present invention that the expression levels of a panel of marker genes including GalNAcT or PAX3 are indicative of melanoma recurrence, disease-free survival, or overall survival (see, e.g., page 25, line 10 – page 30, line 17 of the specification). Without such knowledge, one skilled in the art would not have been motivated to combine Palmieri with Kuo and Scholl to come up with the method of claim 31...Therefore, claim 31 is patentable over the cited art. Claims 32-33, dependant directly or indirectly from claim 31, are also patentable over the cited art for at least the same reasons. The rejections should be withdrawn.".

The arguments filed on 12/15/06 have been carefully considered, but are not deemed persuasive. In regards to the argument that Palmieri does not teach that every marker would be detectable by an RT-PCR assay in histopathologically negative SLN samples, Palmieri et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from sentinel lymph node samples obtained from a patient, using RT-PCR to isolated nucleic acids and amplify mRNA targets from a panel of marker genes comprising MART-1 and tyrosinase (pages 1438-1439, in particular). The methods taught by Palmieri et al comprise methods wherein the sentinel lymph node samples are histopathologically negative for melanoma cells (paragraph bridging

the left and right columns of page 1438). In regards to the argument that neither Scholl nor Kuo indicate that PAX3 or GalNacT would be detectable by an RT-PCR assay in histopathologically negative SLN samples, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Palmieri et al with Sholl et al and Kuo et al by detecting metastatic melanoma cells comprising a method of isolating nucleic acids from histopathologically negative sentinel lymph node samples obtained from a patient, using RT-PCR to amplify mRNA targets from a panel of marker genes comprising MART-1 and tyrosinase as taught by Palmieri et al and amplify other genes associated with metastatic melanoma, including those taught by Sholl et al (PAX3 and MAGE-A3) and Kuo et al (GalNAcT), since Palmieri et al teaches that multiple-marker assays are more sensitive and specific than single-marker assays in detecting metastatic melanoma cells (page 1441 right column, in particular). Further, one of skill in the art would recognize that detecting multiple markers of melanoma metastasis would enhance the ability of one to detect melanoma metastasis due to the heterogeneity of tumor cells. In regards to the argument that there would have been no reasonable expectation of success in detecting PAX3 or GalNacT by an RT-PCR assay in histopathologically negative SLN samples, because for example the level of PAX3 or GalNacT might have been too low to be detected by RT-PCR due to either low expression of the gene or dilution of the marker by other mRNAs, there would have been a reasonable expectation of success in detecting PAX3 or GalNacT by an RT-PCR assay in histopathologically negative SLN samples because Palmieri et al teaches two markers of metastatic melanoma in

histopathologically negative SLN samples (see paragraph bridging the left and right columns of page 1438 of Palmieri et al, in particular). Further, Palmieri et al teaches that multiple-marker assays are more sensitive and specific than single-marker assays in detecting metastatic melanoma cells (page 1441 right column, in particular). In regards to the argument that claim 31 is non-obvious over the cited art because the method of claim 31 has unexpected advantages since it is the discovery of the present invention that the expression levels of a panel of marker genes including GalNAcT or PAX3 are indicative of melanoma recurrence, disease-free survival, or overall survival and without such knowledge, one skilled in the art would not have been motivated to combine Palmieri with Kuo and Scholl to come up with the method of claim 31, claim 31 is obvious over the cited art for the reasons above.

New Rejections

35 USC § 112, second paragraph

Claims 1-7, 10, and 31-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 31, 34, 35 and dependent claims 2, 3, 5-7, 10, 32, and 33 are rejected because claims 1, 31, 34, and 35 recite: "...amplifying nucleic acid targets from a panel of marker genes, wherein the panel comprises GalNAcT, PAX3, or both...". It is unclear what is meant by "nucleic acid targets from a panel of marker genes". It is unclear

whether "nucleic acid targets from a panel of marker genes" means "mRNA transcripts encoded by a panel of marker genes", "genomic DNA comprising a panel of marker genes", "genomic sequences regulated by proteins encoded by proteins encoded by a panel of marker genes", or something else.

Claims 1, 34, 35 and dependent claims 2-7, and 10 are rejected because claims 1, 34, and 35 recite: "...based on the levels of the nucleic acid targets, wherein, as compared to control levels, an increase in the levels of the nucleic acid targets is indicative of an increase in melanoma recurrence, a decrease in disease-free survival, or a decrease in overall survival, and a decrease in the levels of the nucleic acid targets is indicative of a decrease in melanoma recurrence, an increase in disease-free survival, or an increase in overall survival". It is unclear *to what* differences of melanoma recurrence, disease-free survival, or overall survival are predictably "increased" or "decreased".

Claim 1 and dependent claims 2-7 and 10 are rejected because claim 1 recites: "...(a) isolating nucleic acid from a sentinel lymph node (SLN) sample obtained from a melanoma patient; (b) amplifying nucleic acids from a panel of marker genes, wherein the panel comprises GalNAcT, PAX3 or both...". Claim 1 does not distinctly point-out from what sample said nucleic acids are to be amplified. It is unclear whether the nucleic acids which are to be amplified are the same nucleic acids that are to be

isolated from the SLN sample or whether said nucleic acids are to be isolated from some other sample.

Claim 31 and dependent claims 32-33 are rejected because claim 31 recites: "...(a) obtaining a sentinel lymph node (SLN) sample from a melanoma patient, wherein the sample is histopathologically negative for melanoma cells; (b) isolating nucleic acid form the sample; (c) amplifying nucleic acid targets from a panel of marker genes, wherein the panel comprises GalNAcT, PAX3 or both...". Claim 31 does not distinctly point-out from what sample said nucleic acids are to be amplified. It is unclear whether the nucleic acids which are to be amplified are the same nucleic acids that are to be isolated from the SLN sample or whether said nucleic acids are to be isolated from some other sample.

Claim 34 is rejected for reciting: "...(a) isolating nucleic acid from a blood sample obtained from a melanoma patient; (b) amplifying nucleic acids from a panel of marker genes, wherein the panel comprises GalNAcT, PAX3 or both...". Claim 34 does not distinctly point-out from what sample said nucleic acids are to be amplified. It is unclear whether the nucleic acids which are to be amplified are the same nucleic acids that are to be isolated from the blood sample or whether said nucleic acids are to be isolated from some other sample.

Claim 35 is rejected for reciting: "...(a) isolating nucleic acid from a non-sentinel lymph node (NSLN) sample obtained from a melanoma patient; (b) amplifying nucleic acids from a panel of marker genes, wherein the panel comprises GalNAcT, PAX3 or both...". Claim 35 does not distinctly point-out from what sample said nucleic acids are to be amplified. It is unclear whether the nucleic acids which are to be amplified are the same nucleic acids that are to be isolated from the NSLN sample or whether said nucleic acids are to be isolated from some other sample.

New Matter

Claim 35 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **NEW MATTER** rejection.

Claims 35 recites a method of predicting melanoma recurrence, disease-free survival, or overall survival based on levels of nucleic acid targets from a panel of marker genes comprising GalNAcT and PAX3 in non-sentinel lymph node (NSLN) samples. Descriptions of methods of predicting melanoma recurrence, disease-free survival, or overall survival based on levels of nucleic acid targets from a panel of marker genes comprising GalNAcT and PAX3 in non-sentinel lymph node (NSLN) samples are not found in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7, 10, and 31-34 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application No. 11/227575. Although the conflicting claims are not identical, they are not patentably distinct from each other because both instant claims 1-7, 10, and 31-34 claims 1-16 of copending Application No. 11/227575 are drawn to methods of diagnosis of and prognosis of melanoma using identical markers and identical or obvious samples.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600